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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,663	07/15/2003	William Howard Roark	PC25207A	7179

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,663	ROARK, WILLIAM HOWARD	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☒ Claim(s) 1 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/6/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 06, 2004 has been received and acknowledged.

The information disclosure statement filed 02/06/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because item 1 on page 6 of 6 is not a published document. It has been placed in the application file, but the information referred to therein has not been considered as to the merits.

Abstract

Applicant is reminded of the proper content of an abstract of the disclosure.

The following is a quotation from 37 CFR 1.72:
(b) A brief abstract of the technical disclosure in the specification must commence on a separate sheet, preferably following the claims, under the heading "Abstract" or "Abstract of the Disclosure." The sheet or sheets presenting the abstract may not include other parts of the application or other material. The abstract in an application filed under 35 U.S.C. 1 11 may not exceed 150 words in length. The purpose of the abstract is to enable the United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure.
The abstract of the disclosure is objected to because it exceeds 150 words.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Examiner suggest having the

cyclogenase –2 inhibitor that is not celecoxib or valdecoxib be replaced with the specific COX-2 inhibitor.

Claim Objections

Claim 1 is objected to because of the following informalities: The abbreviation COX-2 and MMP-13 should be given as its full name or with the full name in parenthesis therewith when first used. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus

because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In other words, the Applicant has given in the specification on pages 32-34 and 68-155 a lengthy list of MMP-13 allosteric inhibitors, similarly COX-2 selective inhibitors are listed at significant length on pages 35-38. However, claims 2 and 3 the very broad claims which cite the Cartesian coordinates are lacking the corresponding chemical structures.

Claim 5-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid, osteo arthritis, representation of inflammation and joint pains , does not reasonably provide enablement for the treatment of a wide variety of inflammation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the invention: The claimed invention concerns a method of using a pharmaceutical composition comprising that is not celecoxib or valdecoxib and an allosteric inhibitor of matrix metalloprotease 13 or a pharmaceutically acceptable salt thereof for the treatment of a number of diseases, including arthritis, inflammation, cartilage degeneration, and pain.

The state of the prior art: Matrix metalloproteinase 13 is known to be a promising molecular target for anti-arthritis drugs. Its activity in the degradation of the extra-cellular matrix and destruction of cartilage is well known. COX-2 inhibitors are generally known to be useful as a non-steroidal anti-inflammatory drug useful for the relief of symptoms of some types arthritis and other diseases characterized by inflammation. MMP-13 inhibitors are not known to be generally useful in the treatment of a representation of kinds of pain or inflammation. The treatment of pain is a complex art due to the fact that pain can be caused by many different disorders, and no one treatment is universally useful for the treatment of a wide variation of pain. In particular, pain is divided into neuropathic and nociceptive categories, representing pain arising from a disorder of the nervous system and pain arising from a painful stimulus to the nerves, respectively. As described by Woolf et al. (Reference included with PTO-892) drugs used to treat nociceptive pain, including non-steroidal anti-inflammatory drugs such as valdecoxib, are often ineffective against neuropathic pain, such as that arising from nerve injury or diabetes, and vice versa. (p. 1959, left column, second paragraph) According to Woolf et al., "There is no treatment to prevent the development of neuropathic pain, nor to adequately, predictably, and specifically control established

neuropathic pain." (p. 1959, left column, third paragraph). Valdecoxib, as described in US patent 5985902 (reference cited in PTO-892) is useful in a method for treating inflammation and inflammation-related disorders including pain.
(Column 2, line 50 - Column 3, line 12, also Claims 14-21) No mention is made of valdecoxib or related compounds as being useful for the treatment of neuropathic pain or other kinds of pain not associated with inflammation.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictabilitv or unpredictabilitv of the art: While there exist many drugs for the treatment of pain and inflammation, there is no panacea which is capable of relieving all types of pain. Each individual drug for the treatment of pain must be evaluated on its own merits as to the specific cases in which is it or is not useful. Additionally, combinations of drugs may produce interactions between drugs which may either inhibit the desired activities of the drugs being combined or else introduce undesirable side effects.

The Breadth of the claims: Claim 5 includes methods of treating a large representation forms of arthritis, inflammation, cartilage damage, and pain using a combination of COX-2 and a amatrix metalloproteinase 13 inhibitor. No limitations are introduces as to the specific type of inflammation or pain to be treated.

According to Silverman (Chapter 3, pp. 74-86, reference included with PTO-892) the binding of a drug to a receptor, and thus its biological activity, is affected by factors including the spatial arrangement of atoms within the molecule, chirality of the drug, and

geometric isomerism. Groups (Z)n-A-(R2)q and W2 of formula (A) are both inclusive of a broad range of functional groups which vary as to all three of these factors, and thus are expected to possess differing biological properties in addition to their ability to bind and inhibit MMP-13. Additionally, the various compounds may or may not produce deleterious interactions when combined with a cCOX-2 inhibitor.

The amount of direction or guidance presented:

The amount of direction or guidance present is found on pages 178-187 wherein the various formulations where provided. No data of how the treatments of the a representation of the various types of diseases claimed was provided.

The presence or absence of working examples: No working examples are provided for the treatment of any disorder in any subject. IN particular, no working examples are given for the treatment of neuropathic pain. Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped ad such as the pharmacology of matrix metalloprotease inhibitors and the treatment of neuropathic pain. See MPEP 2164.

The quantity of experimentation necessary:

In order to treat neuropathic pain using the claimed pharmaceutical composition, a skilled practitioner of the art would undertake to develop a therapeutic regimen without precedent in the current state of the art. As the applicant's disclosure provides no guidance for the treatment of neuropathic pain, or any pain not associated with inflammation, the development of this therapeutic method would be an independent research endeavor which would present significant obstacles, mainly arising from the fact that neither of the drugs included in the claimed combination is known to affect any

molecular target involved in neuropathic pain. This process would involve the screening of candidate compounds against relevant molecular targets, optimization of lead activity, and validation of lead compounds using in vivo animal models of neuropathic pain. Developing such a therapeutic method without guidance from applicant's disclosure represents an undue experimental burden to one skilled in the art wishing to practice the invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-9 of U.S. Patent Application No. 10619769. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to combinations of a cox-2 inhibitor other than celecoxib or valdecoxib with an allosteric inhibitor of MMP-13, of undefined structure, as well as a pharmaceutical composition and method of treatment of disorders including cartilage damage, inflammation, arthritis, and pain involving said composition The current application claims anticipate the copending application claims.

Both applications recite using the same compositions and/or derivatives thereof. See current application claims 1, 4-9 and copending application claims 3-9. The compositions recited in the claims are obvious of each other.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S.

Patent Application No. 10620173. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to combinations of a cox-2 inhibitor other than celecoxib or valdecoxib with an allosteric inhibitor of MMP-13, of undefined structure, as well as a pharmaceutical composition and method of treatment of disorders including cartilage damage, inflammation, arthritis, and pain involving said composition The current application claims anticipate the copending application claims.

Both applications recite using the same compositions and/or derivatives thereof. See current application claims 1-9 and copending application claims 3-9. The compositions recited in the claims are obvious of each other.

With regards to the Cartesian coordinates in Anstrong, in the instant claimed subject matter the factors including the spatial arrangement of atoms within the molecule, chirality of the drug, and geometric isomerism would have possessed the claimed numerical value when the substituents are the same.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent Application No's. 10619777, 10620174 and 10619662. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to combinations of a cox-2 inhibitor other than celecoxib or valdecoxib with an allosteric inhibitor of MMP-13, of undefined structure, as well as a pharmaceutical composition and method of treatment of disorders including cartilage damage, inflammation, arthritis, and pain involving said composition The current application claims anticipate the copending application claims. The inhibitors other than celecoxib or valdecoxib would have been obvious variations of the instant claimed compounds having different substitution.

With regards to the Cartesian coordinates in Angstrong, in the instant claimed subject matter the factors including the spatial arrangement of atoms within the molecule, chirality of the drug, and geometric isomerism would have possessed the claimed numerical value when the substituents are the same

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Claim Rejections - 35 USC § 103

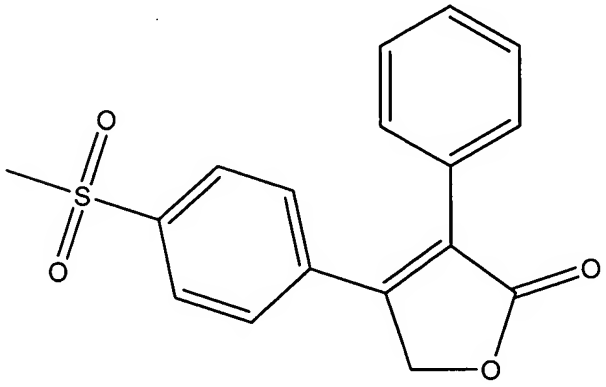
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botting et al. Rheumatology in view of Weithamann et al US 6,933,298.

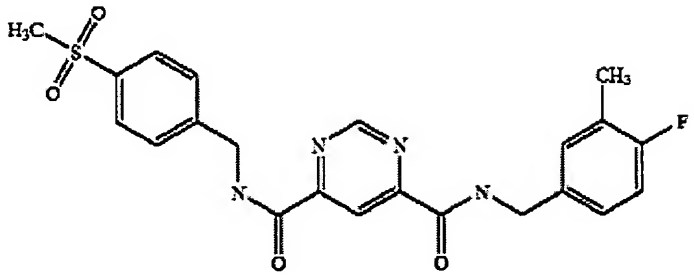
Botting et al. teach the use of rofecoxib



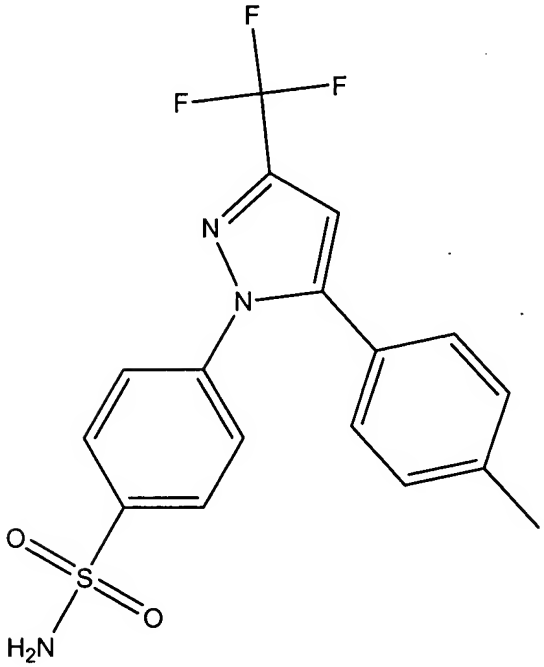
rofecoxib

cyclooxygenase inhibitor (COX- 2) inhibitor of matrix metalloproteinase-13 (MMP-13) see pages 888 and 893. Botting et al teach that MMP inhibitor therapy would be best combined with other therapies directed at different stages of the disease with regards to claims 1, 4-9 of the instantly claimed subject matter.

Weithmann et al. which claims benefit of provisional application 60/358897, filed Feb. 22, 2002, teaches a class of compounds of the structure pictured in figure 1 below:



which is not a



celecoxib

Weithmann et al. also teaches that the disclosed compound are selective inhibitors of matrix metalloprotease 13 which are useful for the treatment of degenerative diseases of the joints. (Col.1, lines 18-23) Specific diseases mentioned as being associated with elevated MMP-13 activity, and treatable by the compounds of Weithmann et al., include, "degenerative joint diseases such as osteoartheoses, spondyloses, chondrolysis following joint trauma or a relatively long period of joint immobilization

following injuries to the meniscus or patella or the tearing of a ligament. In addition they also include diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic diseases of the locomotor system, such as inflammatory, immunologically or metabolism-determined acute and chronic arthritides, arthropathies, myalgias, and disturbances of bone metabolism. (see col. 8, 46-56). Weithmann et al. does not teach a combination of a pyridinedicarboxamide with any other COX-2 inhibitor.

One of ordinary skill in the art would have been motivated to combine these two references in this manner in order to treat cartilage damage associated with arthritis (by administering one of the pyridinedicarboxamides of Weithmann et al) while simultaneously treating pain and inflammation caused by arhritis (by administering rofecoxib). One of ordinary skill in the art would have reasonably expected success because rofecoxib and the compounds of Weithmann et al. were both known to be useful for the treatment of arthritis and were known to act by different mechanisms which could both function simultaneously.

As to claims 2 and 3, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full

para.). Next, the USPTO does not have testing fascilities to analyze such Angstrom parameters compared to the prior art.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Botting et al. Rheumatology in view of Weithamann et al US 6,933,298.as applied to claims 1-9 above, and further in view of Desiraju et al., J. Phys. Org. Chem taken with Rosenblum et al. J. Biol. Chem.

Computational analysis of compounds other than valdecoxib and celecoxib where done by Desiraju et al. showing orientation of rofecoxib (see entire doc, highlightedsections). SC-558. 565608. A potent and selective inhibitor of cyclooxygenase-2 ... MMP-9/MMP-13 Inhibitor II 444253 A piperazine-based potent inhibitor of MMP-13. Page 486, table 3 shows the different hydrogen interactions.

Rosemblum et al. teach the structural basis for binding of MMP-2, although the reference did not specifically teach MMP-13, it however teaches how these inhibitors bind with an S1 (nucleophilic binding) mechanism for the MMPs as stated (see page 27010 highlighted section).

It has been held that it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art.

As to claims 2 and 3, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject

matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full para.). Next, the USPTO does not have testing fascilities to analyze such Angstrom parameters compared to the prior art.

Thus the invention taken as a whole is prima facie obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 9/5/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

SVG

8/22/06